American Journal of Medical Genetics 70:74–79 (1997)

Paternal Uniparental Disomy for Chromosome 14: A Case Report and Review

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Uniparental disomy (UPD) for several chromosomes has been associated with disease phenotypes. Maternal UPD for chromosome 14 has been described and has a characteristic abnormal phenotype. Paternal UPD14 is rare and only three previous cases have been reported. We describe a new case of paternal UPD for chromosome 14 in an infant with a 45,XX,der(13q;14q) karyotype, which was confirmed by molecular analysis. The proposita had findings similar to those of the previous cases of patUPD14 and we conclude that there is a characteristic patUPD14 syndrome most likely due to imprinting effects. Couples with Robertsonian translocations involving chromosome 14 should be counseled as to the possibility of UPD14 and the option of prenatal diagnosis when indicated. Am. J. Med. Genet. 70:74–79, 1997.

KEY WORDS: chromosome 14; uniparental disomy; imprinting; Robertsonian translocation

INTRODUCTION

Uniparental disomy (UPD) occurs when both homologues of a chromosome are inherited from a single parent [Engel, 1980]. UPD may manifest as either heterodisomy (both copies of the same homologue from the one parent) or isodisomy (two copies of one of the homologues from the one parent). Distinct disease phenotypes have been associated with UPD for several chromosomes and are generally considered to be due to the presence of imprinted genes on the chromosomes involved [Ledbetter and Engel, 1995]. Prader-Willi and Angelman syndromes are the best characterized im-

Fig. 1. Appearance of the proposita at 6 months of age.

Contract grant sponsor: Lehman Brothers Inc.

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Received 14 May 1996; Accepted 14 August 1996

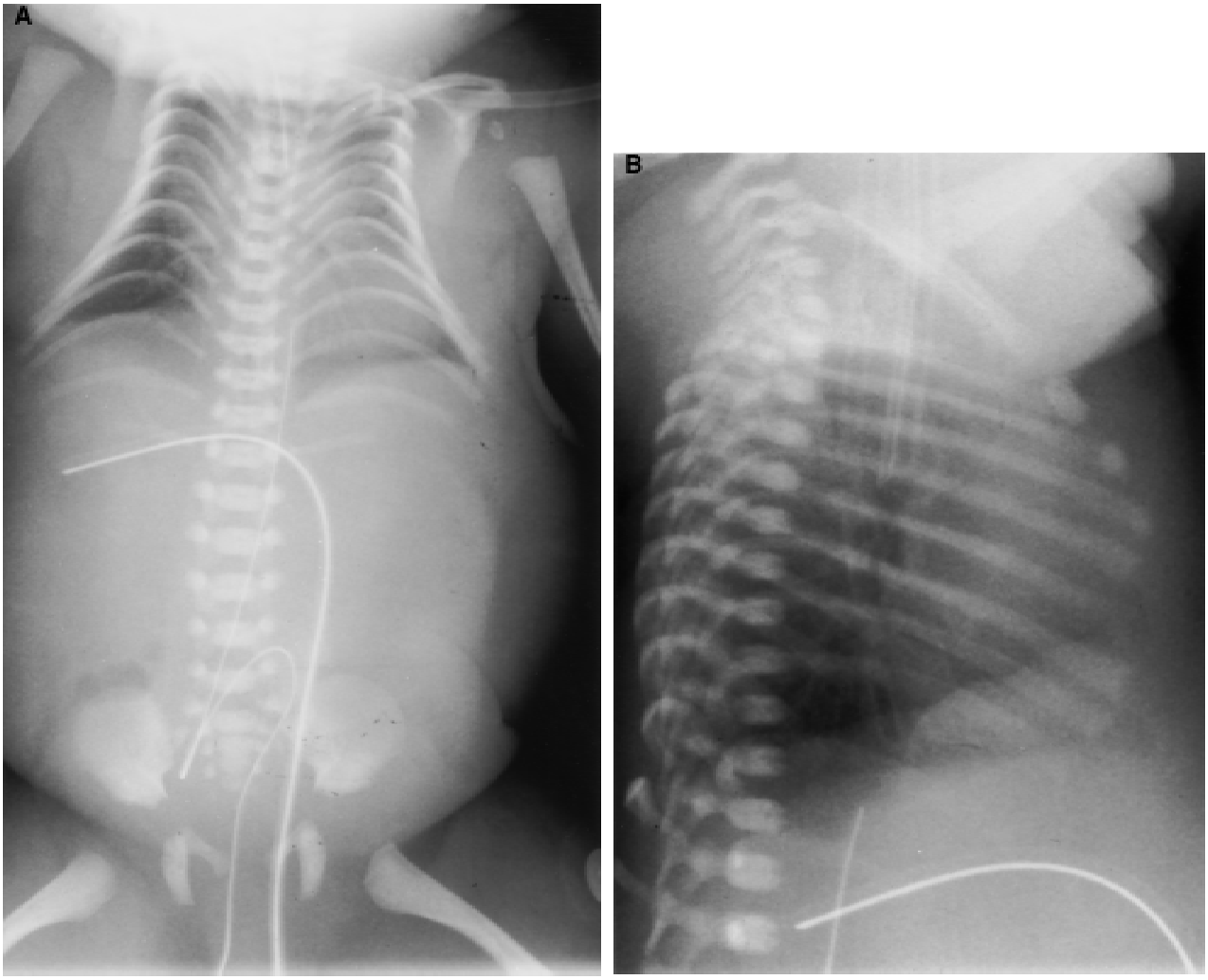

Fig. 2. **A:** AP and **(B)** lateral radiographs demonstrating the small bell-shaped thorax with hypoplastic ribs and elongated clavicles.

printing syndromes and can be caused by maternal and paternal UPD15, respectively [Nicholls, 1993]. In addition, Beckwith-Wiedemann syndrome has been associated with paternal UPD11 [Slatter et al., 1994], and UPD7 and 16 occur in some cases of intrauterine growth retardation [Kalousek et al., 1993; Kalousek and Barrett, 1994]. Where UPD occurs as isodisomy, the phenotype may also be due to homozygosity for a recessive mutation, e.g., UPD7 and cystic fibrosis [Spence et al., 1988; Voss et al., 1989].

Uniparental disomy for chromosome 14 has now been reported in 13 cases: 10 patients had maternal uniparental disomy for chromosome 14 (matUPD14) [Temple et al., 1991; Pentao et al., 1992; Antonarakis et al., 1993; Healey et al., 1994; Morichon-Delvallez et al., 1994; Robinson et al., 1994; Sirchia et al., 1994; Tomkins et al., 1994; Coviello et al., 1995; Papenhausen et al., 1995] and 3 patients had paternal UPD14 (patUPD14) [Wang et al., 1991; Papenhausen et al., 1995; Walter et al., 1996].

Here, we describe a patient with patUPD14. The similarity of physical findings to the previously reported cases is suggestive of a distinct phenotype and is most likely due to imprinting effects.

CLINICAL REPORT

The proposita, a female, was the first born to healthy unrelated parents from Mexico. The mother was 21 and the father 20 years old. The pregnancy was complicated by polyhydramnios and premature labor at 29 weeks gestation. Delivery was spontaneous and vaginal, with Apgar scores of 2 at 1 min and 5 at 5 min. Birth weight was 1,960 g, length was 40 cm, and head circumference was 29 cm. There was generalized non-pitting edema, a short neck, and a small, narrow thorax. Facial anomalies included a depressed nasal bridge, small ears, a protruding philtrum, and short palpebral fissures (Fig. 1). The abdomen was distended and the liver and spleen were palpable 3–4 cm below the costal margin. The baby was hypotonic with a poor suck and required immediate intubation and assisted ventilation with 35–40% oxygen. Multiple attempts to discontinue the supplemental oxygen were unsuccessful, and a tracheostomy was performed for continued assisted respira-

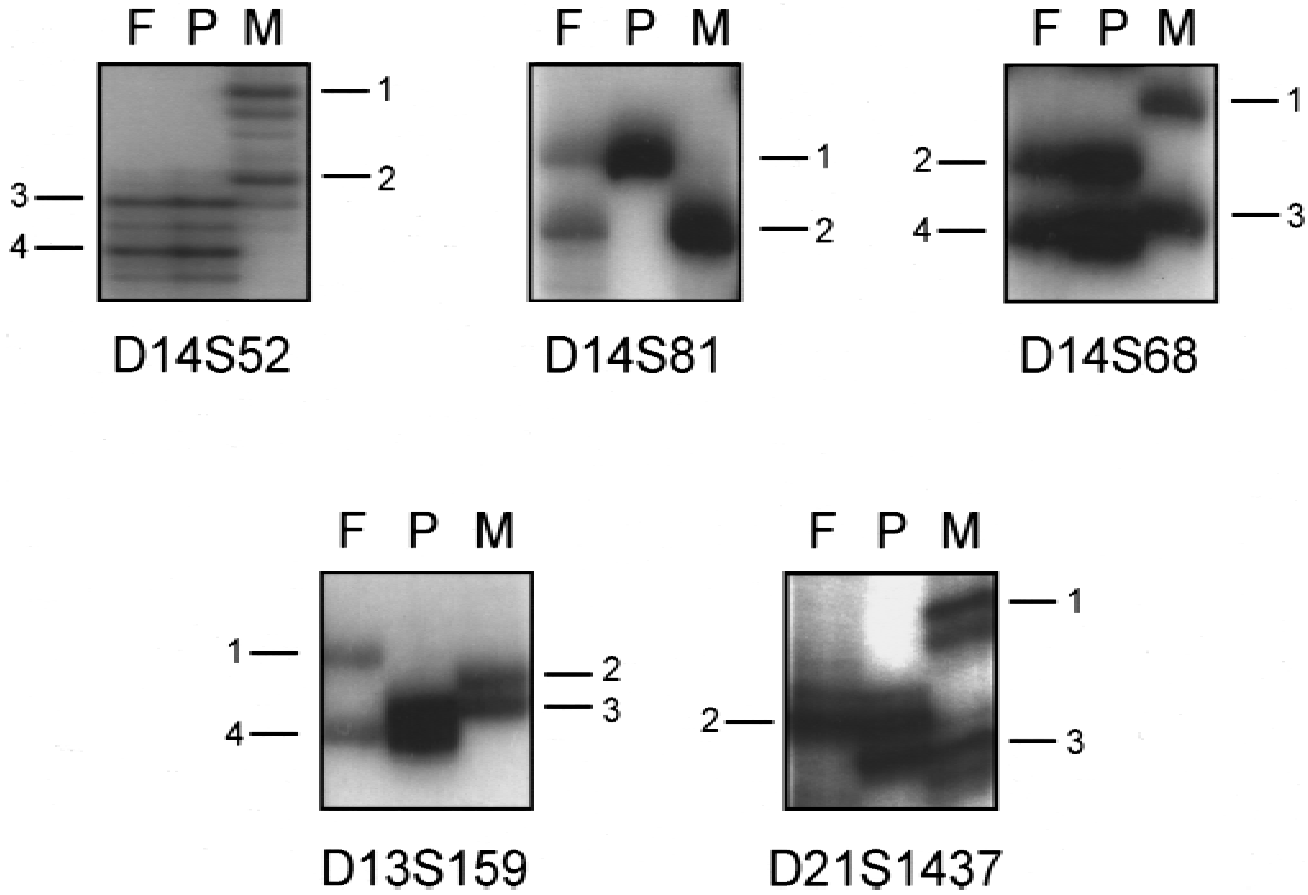

Fig. 3. Polymorphism analysis of the father (F), proposita (P), and mother (M) with chromosome 14 STS and VNTR markers. D14S52 and D14S68 showed paternal heterodisomy, and D14S81 showed paternal isodisomy in the proposita. D13S159 and D21S1437 clearly demonstrated biparental inheritance.

tion, and to allow orogastric feeding. The baby died at age 6 months of pulmonary complications. A skeletal survey showed proportionately short long bones, microcrania, ossification defect of the cranial base, a bell-shaped, short thorax with thin ribs, elongated clavicles, and coxa valga (Fig. 2).

MATERIALS AND METHODS

Cytogenetic analysis was performed on peripheral blood lymphocyte cultures from the proposita and her parents. Genomic DNA for molecular studies was extracted from lymphocytes by standard techniques [Sambrook et al., 1989]. Sequence tagged site (STS) and variable number of tandem repeat (VNTR) markers [Genome Data Base, 1995] on chromosomes 13, 14, and 21 were PCR-amplified as described [Wang and Weber, 1992].

RESULTS

Chromosome analysis from lymphocyte cultures of the proposita showed a female karyotype containing a Robertsonian translocation between chromosomes 13 and 14: 45,XX,der(13;14)(q10;q10). Parental karyotyping identified the same Robertsonian translocation in her father [45,XY,der(13;14)(q10;q10)]. The maternal karyotype was 45,XX,der(14;21)(q10;q10) (data not shown).

Molecular studies using STS and VNTR markers on chromosome 14 showed paternal disomy for chromosome 14, and the absence of a maternal chromosome 14 in the proposita. Paternal heterodisomy was seen with markers D14S52 and D14S68 (Fig. 3) and isodisomy for D14S81 and D14S122. The remaining markers (D14S50, D14S80, D14S306, D14S301, D14S129, D14S583, D14S587, D14S125, D14S77, D14S43, and D14S45) were uninformative but consistent with either paternal isodisomy or heterodisomy (Fig. 4). Biparental inheritance of chromosomes 13 and 21 was shown with markers D13S159 and D21S1437 (Fig. 3).

DISCUSSION

The impact of imprinting and uniparental disomy on human disease has only recently been appreciated. Maternal or paternal duplication or deficiency of imprinted genes has been considered to cause various recognizable syndromes. MatUPD15 is estimated to account for 20–25% of Prader-Willi syndrome patients and patUPD15 for about 5% of Angelmann syndrome patients [Nicholls, 1993]. Similarly, 25% of Beckwith-Wiedemann syndrome patients have patUPD11 [Slat-

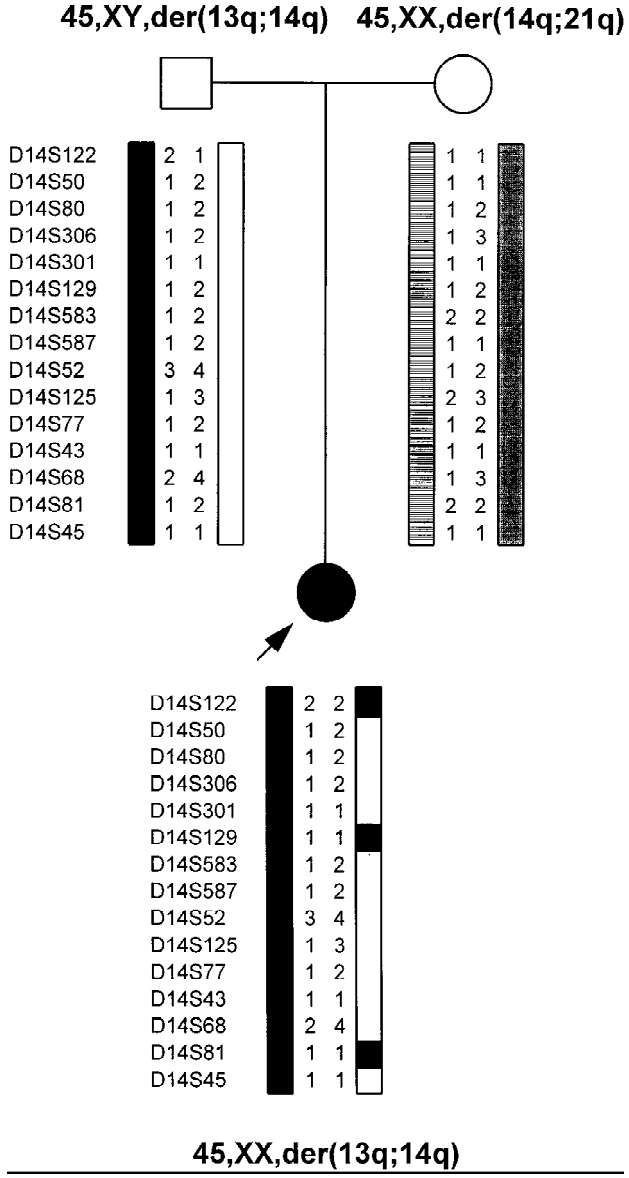

Fig. 4. Haplotype of the proposita and her parents from chromosome 14 STS and VNTR markers. The haplotype of the proposita was consistent with paternal heterodisomy for markers D14S50, D14S80, D14S306, D14S583, D14S587, D14S52, D14S125, D14S77, and D14S68, and isodisomy for markers D14S122, D14S129, and D14S81. It was not possible to distinguish between heterodisomy and isodisomy for markers D14S301, D14S43, and D14S45.

ter et al., 1994]. In addition, intrauterine growth retardation has been associated with confined placental mosaicism and UPD, particularly for chromosomes 7, 15, and 16 [Kalousek et al., 1993; Kalousek and Barrett, 1994].

A distinct phenotype in matUPD14 was suggested by Healey et al. [1994] based on four cases in the literature. Patients with matUPD14 have a phenotype of variable severity characterized by short stature, arrested hydrocephalus, small hands, scoliosis, mild developmental delay, and precocious puberty [Temple et al., 1991; Pentao et al., 1992; Antonarakis et al., 1993; Healey et al., 1994; Robinson et al., 1994; Tomkins et al., 1994; Coviello et al., 1995]. Only two patients with matUPD14 have been reported with normal phenotypes. Morichon-Delvallez et al. [1994] reported the prenatal diagnosis of matUPD14 and the infant was described as normal at birth. Follow-up of this case will determine whether developmental delay, short stature, or other characteristic features develop. The second patient, a 30-year-old woman reported by Papenhausen et al. [1995], also had a normal phenotype. The DNA studies reported were consistent with matUPD14. However, the absence of a paternal control and homozygosity for only two markers do not allow the diagnosis of uniparental disomy with certainty.

Only three patients with patUPD14 have been previously reported [Wang et al., 1991; Papenhausen et al., 1995; Walter et al., 1996]. As shown in Table I, our patient had many of the findings described, i.e., polyhydramnios, characteristic facial anomalies, skeletal anomalies including a small thorax, abnormal ribs, and short limbs. The similarity of congenital abnormalities in the four cases suggests that patUPD14 can be considered the cause of an identifiable genetic syndrome.

Our patient was more severely affected than the previously described cases. This variability could be due to homozygosity for mutations of genes in regions of isodisomy, a complicated course because of extreme prematurity, or undetected mosaicism for trisomy 14. Trisomy 14 mosaicism has a distinct phenotype with psychomotor retardation, narrow palpebral fissures, broad nose, dysplastic and/or low set ears, micrognathia, short neck, congenital heart disease, and genitourinary abnormalities [Fujimoto et al., 1992]. Although mosaicism cannot be completely ruled out, it seems unlikely, since the more characteristic manifestations, i.e., small thorax, abnormal ribs, and short limbs, were not described in mosaic trisomy 14. The oldest living patient with patUPD14 reported was 9 years old [Wang et al., 1991] and had severe mental retardation in addition to the characteristic findings. Long-term follow-up of additional cases will be necessary to determine whether mental retardation is a consistent manifestation in patUPD14.

UPD14 in the proposita was the result of a paternal meiosis-I non-disjunction, since a meiosis-II non-disjunction would have resulted in either two chromosomes 14 or two translocation chromosomes. Although isodisomy for D14S122 (the most centromeric marker in Fig. 4) suggested a meiosis-II event, this was incompatible with the cytogenetic data. The relative positions of D14S122 and D14S50 are unknown, so D14S50 could in fact be the most centromeric marker, which would be consistent with the cytogenetic data. Assuming a disomic 14 sperm, two possible mechanisms could have accounted for patUPD14 in our patient, either gamete complementation or trisomy rescue. Since the mother of the proposita also had a Robertsonian translocation, a maternal non-disjunction resulting in a nullisomic gamete was more likely. This is similar to the parents of the patUPD14 patient reported by Wang et al. [1991] who each had a translocation: 45,XY,der(13q;14q) and 46,XX,t(1;14)(q32;q32). By analogy, mice heterozygous for chromosome translocations are crossed to generate progeny with UPD for

TABLE I. Comparison of Patients With Paternal Uniparental Disomy for Chromosome 14

	Wang et al. [1991]	Papenhausen et al. [1995]	Walter et al. [1996]	Proposita
Karyotype	45,XX,der(13q;14q)pat	45,XX,der (14q;14q)	45,XY,idic(14) (p11;p11)	45,XX,der (13q;14q)pat
Polyhydramnios	–	+	+	+
Hirsute forehead		+		+
Blepharophimosis/short palpebral fissures	+		+	+
Protruding philtrum	+		+	+
Puckered lips	–	+	+	–
Retrognathia		+		+
Small ears	+		+	+
Subarachnoid hygromas	+			–
Webbed neck	+			+
Small thorax	+		+	+
Abnormal ribs	+		+	+
Heart murmur (cardiomyopathy)	–		+	+
Fetal abdominal distension		+		+
Ventral wall hernia	–	+		+
Hepatosplenomegaly	–			+
Gastrostomy/orogastric feed		+	+	+
Undescended testes	N/A[a]	N/A	+	N/A
Short extremities			+	+
Digit contraction		+	+	+, Late
Simian creases	+		+	+

[a]N/A, not applicable.

imprinting studies [Cattanach and Kirk, 1985; Cattanach et al., 1995]. The second mechanism, trisomy rescue, involves the fertilization of a normal ovum by a disomic 14 sperm, producing a trisomy 14 zygote. A post-zygotic non-disjunction or anaphase lag of the maternal chromosome 14 would result in patUPD14. This mechanism was evident in the patients reported by Antonarakis et al. [1993] and Sirchia et al. [1994], where mosaicism for the trisomy 14 line was observed.

Several imprinted genes have been identified from UPD studies in the mouse. Human chromosome 14 is syntenic to mouse chromosomes 12 and 14 [Cox et al., 1995]. No imprinting effects have been identified for matUPD or patUPD of mouse chromosome 14 (syntenic to human 14cen-q12) [Cattanach et al., 1995]. In contrast, mouse chromosome 12 (syntenic to the human region 14q13-qter) is thought to be imprinted [Cattanach et al., 1995]. Therefore, the matUPD14 and patUPD14 phenotypes are most likely due to the altered expression of imprinted genes in the region 14q13-qter. No imprinted genes have yet been identified in this region in mouse or human. However, Walter et al. [1996] suggested several chromosome 14 genes including bone morphogenetic protein 4 that might be candidate genes involved in the skeletal anomalies. Further studies are required to define the exact region of chromosome 14 that is imprinted and to identify the genes in that region.

ACKNOWLEDGMENTS

We thank Dr. Ralph S. Lachman and Dr. David L. Rimoin for reviewing the radiographs, Mrs. Sophie Paciuc for expert technical assistance, and Dr. Christi Walter for helpful suggestions. This study was supported in part by a grant from Lehman Brothers, Inc.

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